MEMORANDUM

TO: FILE

FROM: WENDELL L. STONE

DATE: JUNE 28, 1983

RE: ADVERSE "EXPLANATIONS" OF THE MRFIT MORTALITY RESULTS

The following is a list of suppositions which have, or may be, advanced in arguments against concluding that the MRFIT results indicate a need to reevaluate the concept of risk factors as causally related to coronary heart disease. These suppositions should be kept in mind for briefings with TI on this matter.

1. Reduced actual UC death rates.

The design of the MRFIT, including aspects related to the likelihood of observing a statistically significant difference in CHD death rates between the SI and UC groups, was based in part on a predicted death rate in the UC group. However, the death rates in the UC group were much lower than expected, with a resultant reduced capacity of the trial to demonstrate a death rate difference between the groups.

2. Reduced predicted UC death rates (UC risk factor reductions).

The design of the MRFIT was based on the assumption that the UC group would show zero reductions in serum cholesterol and blood pressure, and only slight reductions in cigarette smoking. However, substantial reductions in these risk factor levels occurred. This reduced the predicted UC mortality rate. As a result, the capacity of the trial to detect a between group difference in mortality rates was diminished.

(Some commentaries on the MRFIT have combined suppositions one and two, to take the form of: Unexpected reductions in UC risk factor levels caused reductions in UC mortality rates, and hence reduced the potential SI/UC difference.)

3. The MRFIT had no control group.

Several commentaries on the MRFIT have emphasized the general point that the UC group was not a control group. In support of this point, specific aspects of the UC experience, as

2501232832

Source: https://www.industrydocuments.ucsf.edu/docs/hnwk0000

described in numbers 1 and 2 above are often cited. However, this issue can be presented more generally in terms of "contamination" of the UC group by widespread changes in the U.S. lifestyle during the 1970s (e.g., increased jogging and weight consciousness and concern over cholesterol levels); further contamination could be said to come from the reported U.S. decline in CHD mortality, and leaving unspecified the sources of this decline.

4. Adverse hypertensive treatment effects.

Hypertensive treatment had an unfavorable effect in certain subgroups (i.e., hypertensives with ECG abnormalities) of the SI men, which offset an overall beneficial effect of intervention. When these subgroups are excluded in the analysis, the relative SI CHD mortality reduction is similar to that predicted at the outset of the trial.

5. Risk factor reduction benefits reach an asymptote.

The CHD risk reduction model used in the MRFIT assumes that risk would decrease as a linear function of risk factor reduction. The MRFIT results do not challenge the position that risk factor reduction is beneficial. Instead, they suggest that the linearity assumption may be incorrect, in that risk factor reduction benefits reach an asymptote. A commentary taking this position would note the reduced risk factor levels and mortality rates in both the SI and UC groups -- then argue that this supports the hypothesis that the risk factor reductions reduced mortality rates, but only up to a point beyond which the relatively greater SI risk factor reductions had a lesser benefit.

6. Confirmation of risk factor status.

It may be true that statistical considerations and unexpected developments in the MRFIT may have left the overall SI/UC comparisons somewhat inconclusive. Nevertheless, the MRFIT results confirm that persons with elevated cholesterol, high blood pressure and cigarette smoking have substantially increased CHD mortality. Thus, the risk factor status of these variables was substantiated. In addition, considering smoking in particular, among those who actually quit there was a very large reduction in mortality, thereby demonstrating the value of intervention.

7. Advanced, but subclinical, atherosclerosis in the sample.

The MRFIT results do not challenge the role of the studied risk factors in causation of CHD. Alternatively, the

2501232833

Source: https://www.industrydocuments.ucsf.edu/docs/hnwk0000

results suggest that middle-aged men who have allowed their risk factors to reach high levels may have already acquired well-developed, largely irreversible atherosclerosis. And the lesson from MRFIT would thus seem to be that more emphasis should be placed on controlling risk factors at an earlier age.

8. Less than anticipated cholesterol reductions.

There are substantial data which suggest that reductions in cigarette smoking and blood pressure may have only minor beneficial effects unless cholesterol levels are also substantially reduced. In view of this, the MRFIT results are not surprising, in that the relative cholesterol reduction in the SI group was only 50% of that specified in the trial design.

9. Interval between risk factor reduction and CHD risk reduction.

CHD risk reduction following risk factor reduction is probably not immediate, and estimation of the "lag" before a substantial beneficial effect accrues is difficult. At the design stage of the MRFIT, it was necessary to make certain assumptions about the "lag" between risk factor change and actual risk reduction. The MRFIT results suggest that the assumptions made about the rapidity of actual risk reduction may have been too optimistic, not that the risk factor reduction hypothesis is wrong.

10. The sample studied was not at high CHD risk.

The MRFIT provides little information on the effects of intervention on high risk men, because the men studied were not actually at high risk. In particular, exclusion criteria applied during screening eliminated the men with the extremes of cholesterol and blood pressure levels, among others. And, aspects of the voluntary recruitment procedure, involving a commitment to a six year trial, ended up selecting a sample of very health-conscious men. This seems clear in that their death rates over six years were substantially lower than the U.S. population as a whole.

WLS/dns

2501232834

Source: https://www.industrydocuments.ucsf.edu/docs/hnwk0000